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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,000	09/09/2003	Michael W. Pantoliano	MNM/002	4943

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,000	PANTOLIANO ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *16-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election of Group I, claims 1-15, with traverse in the reply filed on March 1, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s). In particular, 37 CFR 1.821, which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Thus, each time the human ACE-2 appears in the specification or in the claims, it should be accompanied by a sequence identification number (see for example, page 1, line 11, page 6, line 30, Figure descriptions of Figures 5A, 6, 8A, page 87, line 17, page 89, line 16, and claims 6, 7, 14, and 15). All specific amino acid residues from proteins found in the sequence listing should be accompanied with a sequence identification number of said the protein. Applicants should be reminded that Tables containing the atomic coordinates in Figures 1-3 represent disclosure of amino acid sequences and therefore, a sequence identifier should be in the heading or the Figure description of each Table.

The disclosure is objected to because of the following informalities: Through out the specification, the full length human ACE2 is identified as SEQ ID NO: 4, which is incompatible with the description, see for example paragraph 22 at page 9. SEQ ID NO: 4 is 595 amino acid residues, and there for it can't comprise residues 19-740.

Appropriate correction is required.

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Figure 5B is of poor quality and the examiner can't see the two chains being compared and the differences between them. The examiner is suggesting having one chain in black and the other in white or some other similar distinction. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7 and 9-15 are directed to all possible crystals of an angiotensin-converting enzyme-related carboxypeptidase isolated from any biological or man-made source. Claim 8 is directed to any angiotensin-converting enzyme-related carboxypeptidase isolated from any biological or man-made source. The specification, however, only provides a single representative species of these crystals, containing a protein which it amino acid sequence is not identified or confusing. It is, presumably, consisting of residues 19-740 of SEQ ID NO: 4, or protein resulting from the expression of residues 1-740 of SEQ ID NO: 4 in SF9 cells using baculvirus vector, but SEQ ID NO: 4 is only 595 amino acid residues (please clarify). The native crystal and the crystal containing the inhibitors contain the same protein, and are essentially the same crystal' monoclinic crystal in space group C_2, with very similar unite cell dimensions with variation of about 5%. No other protein is disclosed or described in the specification, which was not taught in the prior art. There is no disclosure of any particular relationship between the native or complexes with inhibitors crystals obtained and the crystallization conditions. It should be noted that the three crystals described in the specification at pages 89 and 90 are obtained under different crystallization condition. Also, there is no disclosure of a structure-activity relationship between the protein consisting residues 19-740 of SEQ ID NO: 4 and its carboxypeptidase activity. The specification also fails to describe additional representative species of these crystals and angiotensin converting enzyme related carboxypeptidase by any identifying structural characteristics or properties other than the space group and unit cell dimension cited in the specification or the amino acid sequence of residues 19-740 of SEQ ID NO: 4, respectively, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible crystals

comprising any native of angiotensin converting enzyme-related carboxypeptidase (ACER-CP) from any source, or in a complex with any inhibitor. Claim 8 is directed to any ACER-CP. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any possible crystals comprising any native of angiotensin converting enzyme-related carboxy-peptidase (ACER-CP) from any source including fusion proteins, or in a complex with any inhibitor. Claim 8 is directed any ACER-CP from any source. The specification provides guidance and examples in the form of an assay to obtain ACER-CP obtained by the expression of residues 1-740 of SEQ ID NO: 4 in CF9 cells, and crystallize the glycosylated protein in the presence and absence of inhibitors 2 and 4 (see example 6). While molecular biological techniques and genetic manipulation to make any protein and synthetic method to make any inhibitor are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of proteins and their complexes is lacking. Also, lacking is knowledge of all possible ACER-CP activity and their enzymatically active mutants and analogues. It is well established in the art that obtaining a protein and its inhibitor complexes in a crystal form is highly unpredictable. The skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization condition, it mutants and complexes may or may not crystallize under the same condition. It should be noted that while the native crystal and the crystal containing the inhibitor-2 and -4 contain the same protein, and are essentially the same monoclinic crystal in space group C_2, with very similar unite cell dimensions that vary within about 5%, the three crystals grow under different conditions, see pages 89 and 90. Proteins containing a trans membrane protein such as that of SEQ ID NO: 4 are, in particular, difficult to crystallize, and that is the reason f0r removing the trans membrane domain of ACER-CP, see example 1 in the specification. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallized. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a ACER-CP protein from a biological source or their mutants which can be crystallized, and identify a crystal suitable structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of gene, cDNA or man-made DNA libraries, and crystallizations conditions or mutants which can be crystallized where the expectation of

obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the exact amino acid sequences to be crystallized, and the crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrases "angiotensin-converting enzyme-related carboxypeptidase" in claims 1-3, 6-9, 11, 14, and 15, and "homologue thereof" in claims 1-3, 9, 11, and 15 render the claims indefinite because the resulting claims do not define the metes and bound of the patent protection desired. For examination purposes, the two phrases are taken to mean any angiotensin converting enzyme and any carboxypeptidase, respectively.

(b) Claims 6, 7, 14, and 15 are indefinite because they are not in compliance with sequence rule. Insertion of a sequence identification number would obviate this rejection.

(c) Claims 4, 5, 10, 12, and 13 are included because they are dependent on rejected claim and do not cure its deficiencies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-3, and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim *et al.* (IDS reference: Biochemistry 1991, 30, 8171-8180).

The phrase "angiotensin-converting enzyme-related carboxypeptidase or homologue thereof" in the claim makes the claim reads on any crystalline carboxpeptidase A, which has been crystallize in the mid 1960's, and the X-ray structure was published in 1968, see Lipscomb *et al.* in the reference list of Kim *et al.* In particular, Kim *et al.*

teach crystals of carboxypeptidase A bound to two chemical entities shown in Figure 1, the first and third structure. They teach the two complexes formed orthorhombic crystals in space group $P2_12_12_1$, see page 8172, right column, second paragraph.

Claim 8 are rejected under 35 U.S.C. 102(b) as being anticipated by U. S. patent 6,194,556 ('556).

The '556 patent teaches human angiotensin converting enzyme-2 (ACE-2) of SEQ ID NO: 2 shown in Figure 1. In Figure 1, the signal peptide is under lined (residues 1-18) and the trans membrane domain is boxed (residues 341-365). Residues 19-613 of SEQ ID NO: 2 in the '559 patent are identical to SEQ ID NO: 4 of the instant application. Also, the '556 patent teaches the expression of ACE-2 in COS cells, see example 5.3. In addition, the patent teaches a water-soluble protein having residues 19-740 of SEQ ID NO: 2 in the patent (claim 8).

Claim 8 are rejected under 35 U.S.C. 102(b) as being anticipated by U. S. patent WO 00/70032 ('032).

The '032 patent document teaches human angiotensin converting enzyme-2 of SEQ ID NO: 2 and named it Zace2 and identifies residues 1-18 as the signal peptide, as well as two murine Zace2 having the amino acid sequence of SEQ ID NO: 6 & 9, see the last paragraph at page 2 through line 23 of page 3. Also, they teach the trans membrane domain of residues 739 to 761 of SEQ ID NO: 2, see page 4, lines 21-32. At page 41, the '032 document teach the recombinant production of the Zace2 protein and their expression as fusion proteins for easy purification (claim 8), see page 41, line 26 through page 51 line 2.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 8 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 6,884,771 ('771). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the patent encompass the embodiment of claim 8. It should be noted that SEQ ID NO: 2 of the patent comprises the amino acid sequence of SEQ ID NO: 4, which is identified as ACER-CP.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656